HYPOTHALAMIC CONTROL OF COOLING RATES IN SURGICAL HYPOTHERMIA

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HYPOTHALAMIC CONTROL OF COOLING RATES IN SURGICAL HYPOTHERMIA

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DEDICATION

TO

Dr. William W.L. Glenn

For his continued interest, patient guidance, and devotion to medical research and teaching.

TO

My wife, Virginia

For her active interest and invaluable assistance in the preparation of this manuscript.

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Dr. Harold T. Hammel, for his generosity in allowing the use of the facilities of the John B. Pierce Laboratory of Hygiene and for his invaluable advice and guidance during the Part II phase of these experiments.

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INTRODUCTION

The role of the central nervous system in the induction of hypothermia is as yet poorly understood.[18,27] Basic to the understanding of this role is a knowledge of the temperature-controlling influences exerted by the anterior and posterior hypothalamic centers. The physiology of temperature regulation has been reviewed by Hardy.[13] He had demonstrated that, although normally the temperature-control centers precisely maintain the body temperature at or near 37° C., under certain conditions these centers can be reset to maintain the body at a different temperature.

The mechanisms of blood flow and thermal exchange at the body surface are not well understood. However, Mellinger and others have substantiated the fact that heat exchange at the body surface is the important factor during the induction of hypothermia.[19] A lack of blood circulating through the body surface reduces the cooling rate, whereas maximal skin blood flow transforms the body shell into a good heat exchanger.

It is well known that when an anesthetized animal is subjected to surface cooling his cutaneous blood flow markedly decreases. This decreases the effective rate of heat loss. It is easy to perceive that if cutaneous blood flow could be maintained at a maximal

level, the rate of heat transfer to the skin would be maximal and the rate of heat loss to the environment therefore maximal.

Many experimenters have shown that, under physiologic conditions, when the hypothalamic centers for temperature regulation "perceive" that the temperature of the blood perfusing the hypothalamus is greater than the set temperature, effector mechanisms are stimulated to increase the rate of heat loss. One of these mechanisms is peripheral vasodilatation. It was our hypothesis that if, at the same time that an animal's surface was being cooled, its temperature-control centers were perceiving a temperature greater than the set point, cutaneous blood flow might be increased due to peripheral vasodilatation rather than decreased due to peripheral vasoconstriction. The net result would be a greater rate of heat loss, which would be very simple to measure and would clearly demonstrate the effect, if any, of alteration of the hypothalamic temperature on the rate of inducing hypothermia in animals by means of surface cooling.

The following experiments were undertaken in an attempt to improve the rate of inducing hypothermia in anesthetized, surface-cooled animals by achieving maximal peripheral blood flow rates. According to our hypothesis, peripheral blood flow would be maximal if, while the

animal was being cooled, its hypothalamus were being perfused at a temperature significantly above normal body temperature. In order to test this hypothesis, the animals used in the following experiments were chronic preparations in which hypothalamic thermodes had been implanted several months previously.

METHODS

GROUP I

Twelve mongrel dogs weighing 13 to 19 Kg. (mean: 15.2) were anesthetized with Nembutal, intubated, and their respiratory rates maintained at 14 to 16 per minute. Thermistor probes were inserted 9 to 10 cm. into the rectum and into the esophagus to the level of the left atrium. Probes were also attached to the inside bottom of the metal tub in which the dogs were placed and to the bubble trap on the heat exchanger. The dogs were placed in the metal tub with only their heads outside the tub. All temperatures were recorded using a YSI Telethermometer,* with an accuracy of plus or minus 0.15° C. and a readability of plus or minus 0.05° C. over the entire range.

Under aseptic conditions, the right common carotid artery of each dog was exposed proximal to the cricoid cartilage. The dogs were heparinized (3 mg./Kg.) and the artery was then opened. A right-angled glass cannula was inserted proximally into the brachiocephalic artery and a curved metal one inserted distally. When the cannulae were in place, the Sigmamotor pump was started.** The sequence of the perfusion system was as follows: proximal common carotid artery to pump to heat exchanger

*Model 46 TU; supplied by Macalaster Bicknell Company
**Model T6S

to distal common carotid artery. A fin-type heat exchanger with an outer jacket was used.[9] The priming volume of the heat exchanger with its attached bubble trap and tygon tubing was 420 ml. The priming solution used was dextrose in saline (5% W/V) with 1 per cent heparin added. The blood flow was regulated to one-eighth the estimated cardiac output. The pump, previously calibrated with water, was set at this calculated flow rate and maintained at this setting throughout the experiment.

The water lines were connected to the heat exchanger in a counter-current direction. A water flow of 16 L./Min. was maintained simply by house water pressure. Temperature was controlled by a Powers Mixing Valve. Since the heat exchanger had an outer jacket (tube), water passed through both an inner and an outer tube and blood passed between them. The maximum water temperature at any time was 42° C., the minimum 25° C.

As soon as the perfusion system was in operation, baseline temperatures were recorded, then the tubs were filled with ice. Each dog was cooled to a rectal temperature of 30° C. or to the temperature above 30° at which the rectal temperature became stable.

Six control and six experimental dogs, chosen by random selection, were used. In the control dogs, the temperature of the right carotid blood passing through

the heat exchanger was regulated to match the esophageal temperature while in the experimental dogs, the right carotid blood temperature was maintained at a mean level of 40.6° C. throughout cooling. This difference in the temperature of the blood contributing to the cerebral blood flow was the only difference between the control and experimental dogs.

During rewarming, the tub was filled with water of a mean temperature of 42.5°C. The right carotid blood temperature in the control dogs was again matched with the esophageal temperature and in the experimental dogs was set and maintained throughout rewarming at 4 to 5° C. below the rectal temperature. All the dogs were rewarmed to a rectal temperature of 37° C. or to the rectal temperature below 37° C. at which the temperature became stable. Ten of the dogs survived the procedure without difficulty. Two other dogs died due to early technical difficulties.

GROUP II

All Part II experiments were done in the laboratories of the John B. Pierce Foundation of Connecticut, Inc., New Haven, Conn. Five mongrel dogs weighing 11 to 15 Kg. (mean: 13.3) were used in whom hypothalamic thermodes had been implanted* from 2 to 12 months previously.

*By Dr. Harold T. Hammel of the Pierce Foundation

The integrity of the temperature-regulatory systems of these animals had been verified in previous experiments with these dogs by Dr. Hammel and his group. The following procedure is described in detail elsewhere.[11] In brief, the thermodes implanted around the hypothalamus act as re-entrant tubes both for the measurement of the hypothalamic temperature on the insertion of a thermocouple into the bottom of the tube, and for thermal stimulation of the hypothalamus on their being perfused with water. Two parallel rows of thermodes were used, each 4 mm. from the midline. The front pair of thermodes was approximately 6 mm. anterior of the anterior commissure and the most posterior pair approximately 3 mm. posterior of the anterior commissure (Diagram 1). An acrylic plate, which formed the bottom of the double-chambered circulator which during thermal stimulation was mounted above the animal's head, was left permanently attached to the thermodes and guides by an epoxy resin. The three anterior pairs of thermodes were perfused with water from the circulator and a thermocouple was placed in one of the posterior pairs to measure hypothalamic temperature. Water from a constant temperature bath (plus or minus 0.05°) was circulated through the upper chamber of the head circulator at a high rate; the water flowed to the tip of the thermode when the lower chamber was connected to a vacuum line.

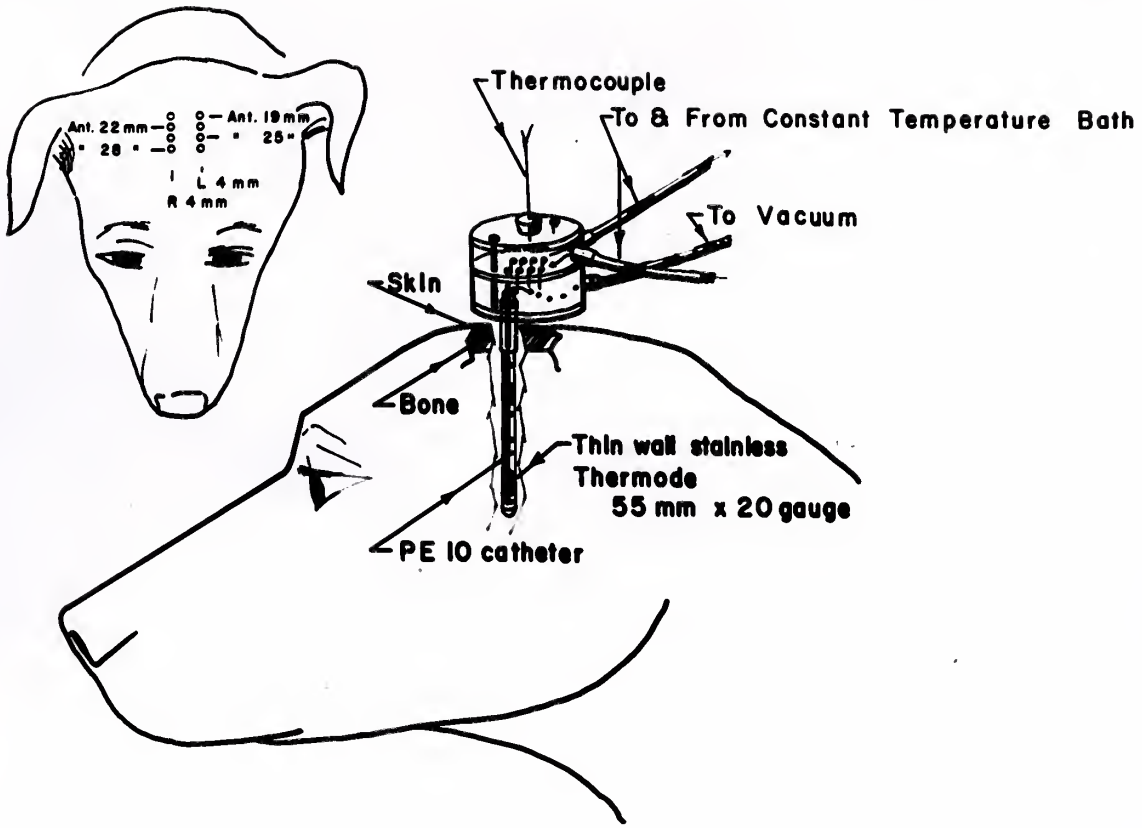


Diagram 1

Details of thermode (or re-entrant tube) and circulator construction. The circulator is shown in place for thermal stimulation of the hypothalamus. Only the lower acrylic plate or bottom of the circulator is left permanently attached to the thermodes and guides by epoxy resin. Taken from Technical Documentary Report, No. AMRL-TDR-63-5, 1963, by H.T. Hammel, et al.[11]

The experimental protocol was designed as follows: each dog was to be cooled and rewarmed three times. For cooling, three methods were used: (1) cooling initially, then, at an arbitrary point during the cooling (33.8° C.), perfusion of the hypothalamus with water of a mean temperature of 43.6° C. (as measured in the upper chamber of the head circulator); (2) perfusion of the hypothalamus initially with water of a mean temperature of 43.6° C., with cooling started ten or more minutes later; (3) with no hypothalamic perfusion whatsoever. Three dogs underwent all three types of cooling but due to unrelated technical difficulties, the two remaining underwent only the first type. As soon as the body had cooled to 32.1° C. (rectal temperature), rewarming was begun by replacing the ice in the bath with warm water of a mean temperature of 40.5° C. and continued until the temperature, rectally, was 37° C. Rewarming was done in the three following ways: (1) with no perfusion of the hypothalamus (control rewarming); (2) with perfusion of the hypothalamus with water of a mean temperature of 32.9° C. as measured in the head circulator; (3) with perfusion of the hypothalamus with water of a mean temperature of 43.6° C. The three dogs who were used for all three types of cooling were also used for the three types of rewarming; only rewarming with no perfusion

of the hypothalamus was done in one of the two other dogs and only rewarming with perfusion with water of a mean temperature of 32.9° C. was done in the other.

In order to test the reproducibility of the results, one dog was again subjected to cooling with hypothalamic perfusion beginning at 33.8° C., and to control rewarming. It is interesting that one of the dogs gave birth to a healthy litter six weeks following one episode of cooling and rewarming and a second dog to a healthy litter two weeks after the last of three successive episodes of cooling and rewarming.

All dogs were anesthetized with intravenous sodium pentothal and maintained at a level of anesthesia sufficient to inhibit all visible shivering. A probe was inserted into the rectum to a depth of 9 to 10 cm. and another into the esophagus to the level of the left atrium. Following the placement of the dog in the tub, with its head and hind feet supported above the tub, thermistors were placed on an ear lobe and a hind foot pad of each dog; these thermistors were held in place and insulated from the room air with collodion. Temperatures were thus measured only on skin not exposed to the ice or warm water.

Two temperature recording instruments were used: the YSI telethermometer and a potentiometer.* The accuracy and readability of the YSI telethermometer was

*Leeds & Northrup Company, Model 8662

described previously in the Group I experiments. The accuracy of the potentiometer was plus or minus 0.1° C., with a readability of plus or minus 0.05° C.

The circulator cap was fastened on the head of each dog and attached to a constant temperature bath. The temperature of the water was measured in the water bath as well as in the upper chamber of the head circulator. A thermistor was inserted through the circulator into one of the stainless steel guides to measure a representative hypothalamic temperature. Rectal, esophageal, skin (pinna and foot pad), hypothalamic, ambient air, circulator water, and tub water temperature were monitored throughout cooling and rewarming. All animals tolerated well each episode of cooling and rewarming.

RESULTS

Group I

Rectal temperatures were used in comparing the two groups of dogs. Figure 1 shows the rates of cooling for the control dogs and Figure 2 for the experimental dogs.

The slope of each curve in degrees centigrade per minute was calculated; the range used for calculation was from the time at which the rectal temperature began to fall (zero time) to the point at which it reached 30° C. Similarly, for rewarming, the range used was from the point at which the rectal temperature began to rise to the point at which it reached 37° C. or until the slope became zero. The rates of cooling and rewarming were corrected for body surface area since the rate of heat transfer between the skin and the environment is proportional to body surface area.[16] The formula for body surface areas used in Group I* is not as accurate as the one used in Group II, for the latter one includes the factor of the animal's length. However, this measurement was not available for use in Group I. Tables 1 and 2 show the results of cooling and rewarming of the control and experimental dogs,

*$A = KW^{2/3}$ A= body surface area, in square centimeters
K= constant= 11.0
W= weight, in grams

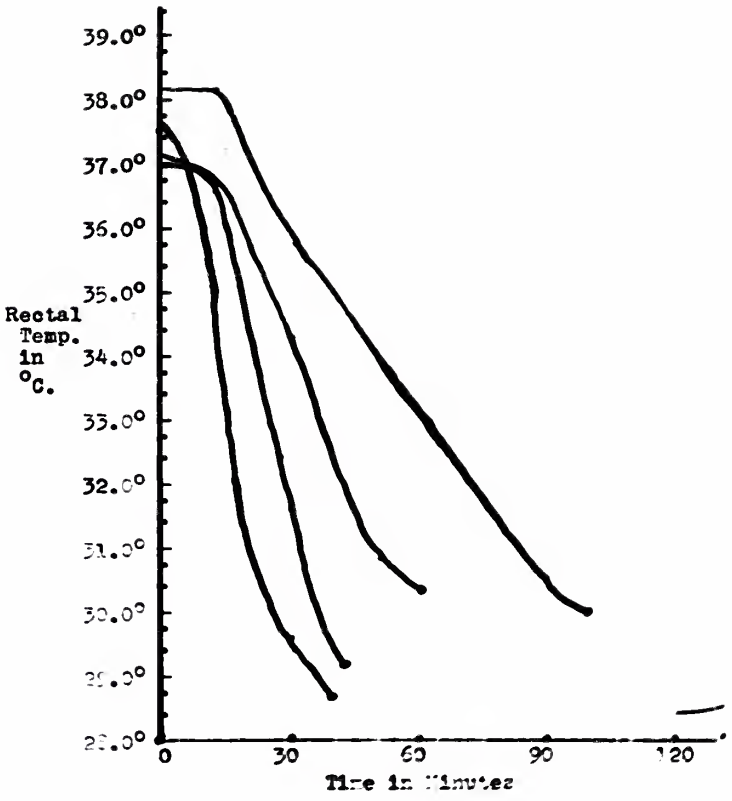


Figure 1

Rates of cooling for Part I control dogs.

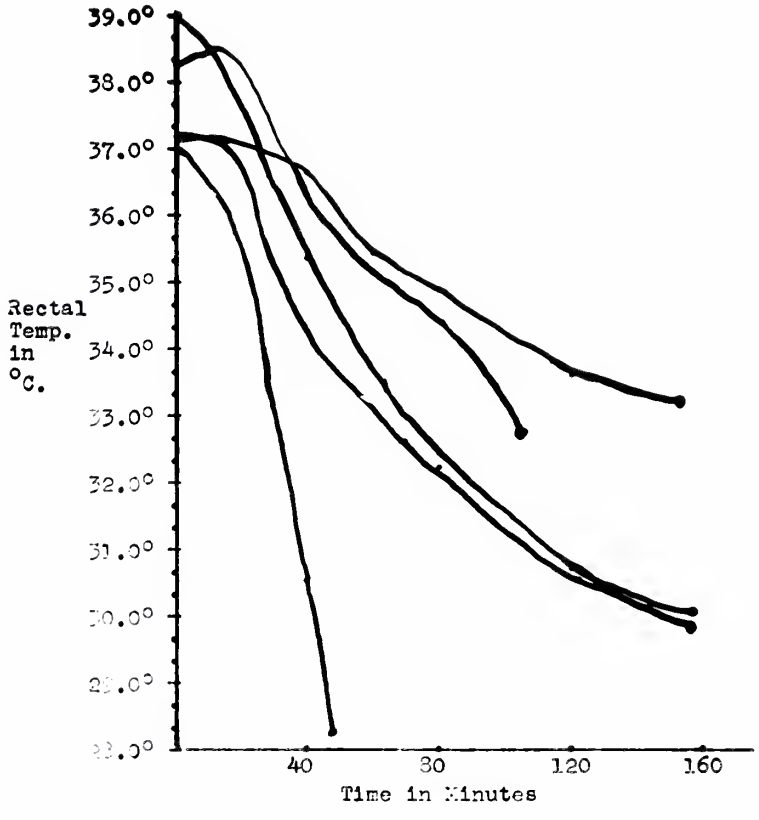


Figure 2

Rates of cooling for Part I experimental dogs.

Dog No.	Weight in Kg.	Area in M^2	Rate of Cooling in $^{o}C./Min/M^2$	Rate of Rewarming in $^{o}C./Min/M^2$
1	13.7	.63	.32	.17
2	18.8	.78	.15	.14
3	14.0	.64	.15	.14
4	13.0	.61	.42	.16
Mean Value	14.9	.66	.26 (S.D.=.13)	.15 (S.D.=.03)

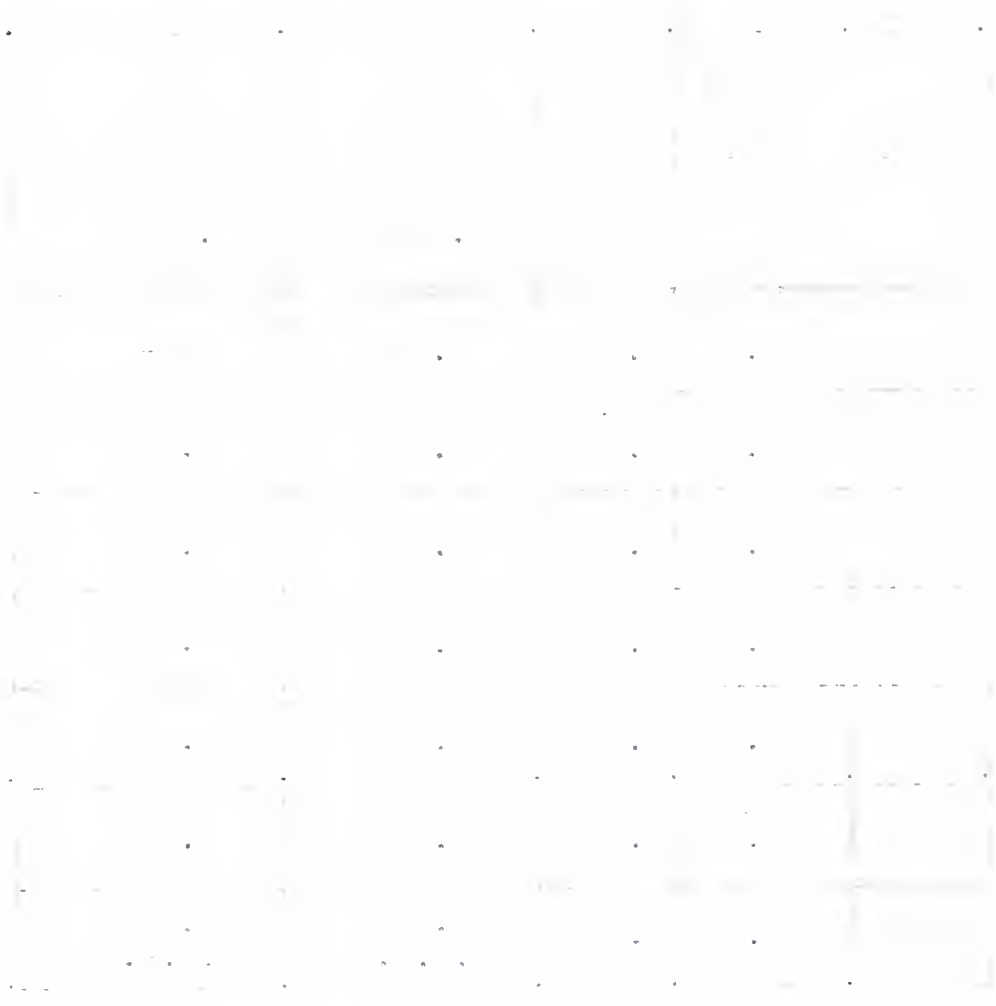
Table 1

Results of cooling and rewarming of Part I control dogs.

Dog No.	Weight in Kg.	Area in M^2	Rate of Cooling in $^oC./Min/M^2$	Rate of Rewarming in $^oC./Min/M^2$
1	15.6	.69	.08	---
2	12.9	.60	.07	.11
3	14.0	.64	.31	.05
4	14.6	.66	.09	.09
5	19.1	.79	.07	.04
6	16.0	.70	.04	.08
Mean Value	15.4	.68	.11 (S.D.=.09)	.07 (S.D.=.03)

Table 2

Results of cooling and rewarming of Part I experimental dogs.



respectively.

The mean rate of cooling for the experimental dogs was 0.11° C. (S.D.=.098) and 0.26° C. (S.D.=.013) for the control dogs. Thus, the experimental dogs cooled at a slower rate than the control dogs. The difference, however, was not statistically significant, P being greater than .05. As shown in the tables, the control dogs rewarmed at a faster rate than the experimental dogs, which difference was statistically significant, P being less than .01.

Group II

The rates of cooling were calculated for each experiment, using rectal temperatures. As in Group I, all rates of cooling were corrected for body surface area. However, since the dogs in this group were available for measurement, a more reliable formula could be used.* The weights and body surface areas of the dogs are shown in Table 3.

The rectal and esophageal temperatures paralleled each other quite closely. In the control experiments the hypothalamic temperatures also closely paralleled the rectal and esophageal temperatures. The skin temperatures usually began at a relatively high level,

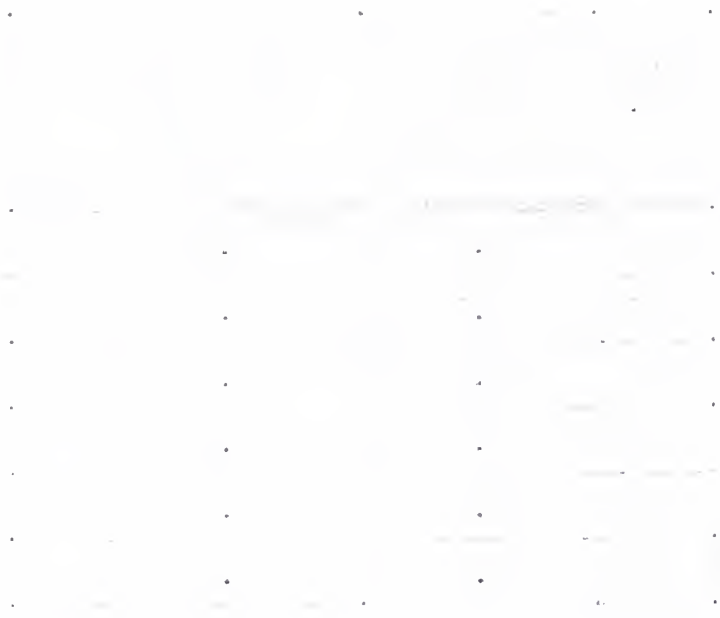
*Cowgill-Drabkin Formula: $A = .002923 \times W^{.37} \times L$

A= body surface area in square meters
W= body weight in kilograms
L= tail base to snout length in centimeters

Dog No.	Weight in Kilograms	Body Surface Area in M^2
1	12.3	.50
2	11.1	.44
3	14.5	.51
4	13.0	.56
5	15.1	.57
Mean	13.6	.51

Table 3

Weights and body surface areas of dogs in Part II.



indicating initial peripheral vasodilatation, but fell rapidly as cooling progressed. However, there was no consistent pattern in the way the skin temperatures responded to cooling and rewarming and though they graphically depicted the progression of peripheral vasoconstriction as the animals cooled, they contributed nothing to the analysis of the results. In general, the results of cooling and rewarming each dog, in terms of the relationship of the various temperatures recorded, were relatively consistent. The results obtained in dog #3 are shown in Figures 3 through 6. As is shown in these graphs, one part of the experiment was repeated. This was done for two reasons: (1) to demonstrate the reproducibility of the results, and (2) to demonstrate that the sharp change in the ear skin temperature (which was almost exactly duplicated) was not related to the change in hypothalamic temperature. Figures 7 through 9 show the results obtained from rewarming one of the dogs.

Table 4 compares the rates of cooling of the three different methods of cooling used. The esophageal temperature usually fell faster than the rectal temperature and the foot pad temperature faster than the ear skin temperature. Table 5 compares the rates of rewarming of the three different methods of rewarming used. The esophagus rewarmed at a faster rate than

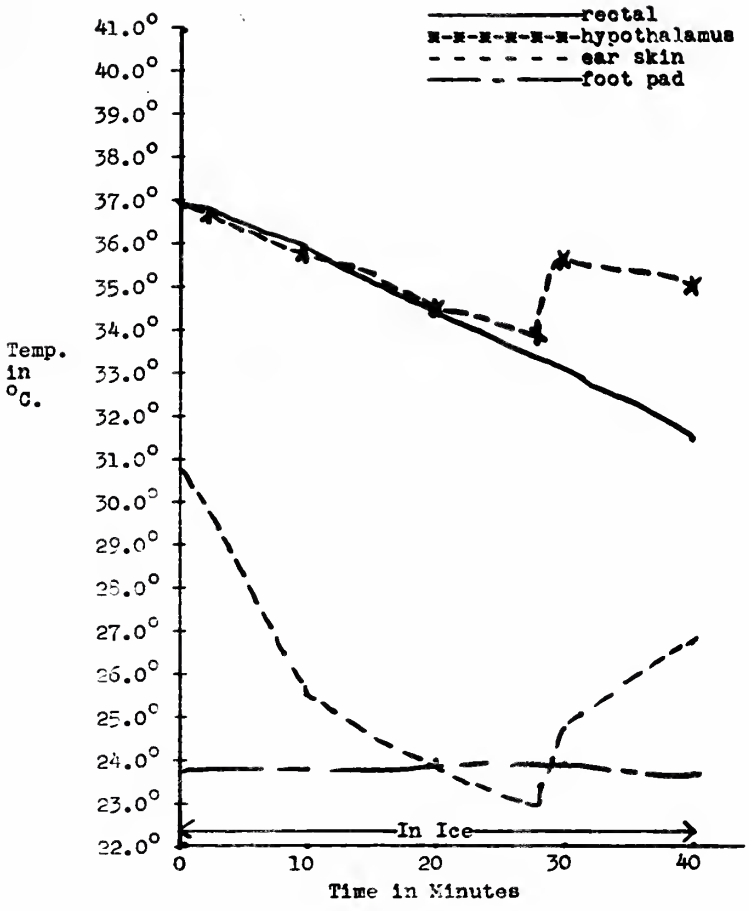


Figure 3

Cooling with initiation of hypothalamic heating during hypothermia. Hypothalamus perfused with water of 44.1° C. from 28 minutes until termination of cooling at 40 minutes.

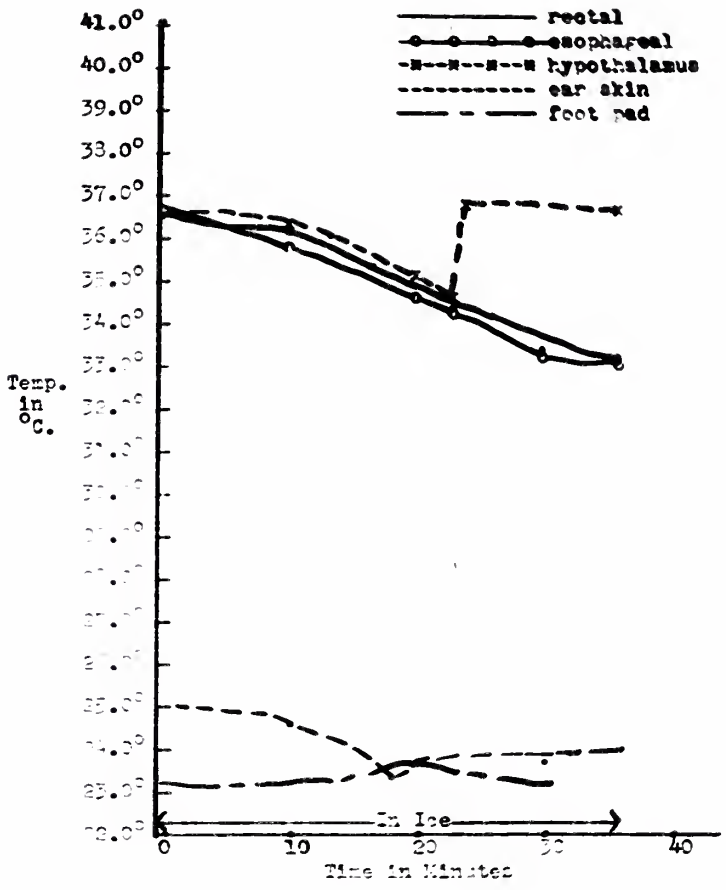


Figure 4

Repeat study with the same dog and in the same manner as in Figure 3. Hypothalamus perfused with water of 43.7° C. from 23 minutes until termination of cooling at 36 minutes.

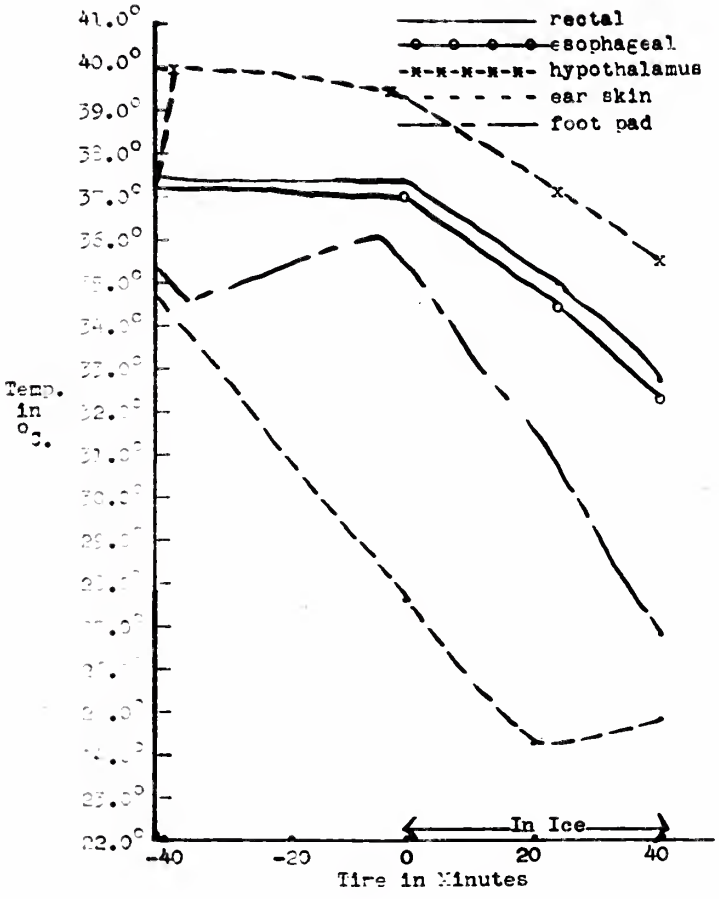


Figure 5

Cooling with initiation of hypothalamic heating with water of 43.6° C. 40 minutes prior to onset of hypothermia and continued until termination of cooling at 40 minutes. Same dog as in Figures 3 and 4.

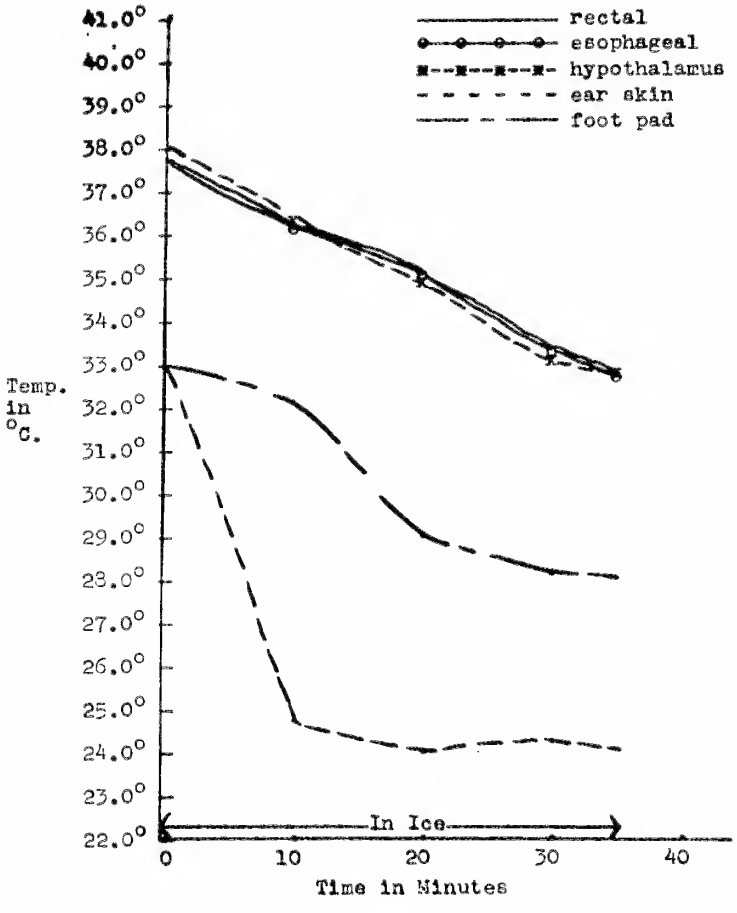


Figure 6

Cooling with no hypothalamic perfusion (control cooling). Same dog as in Figure 5.

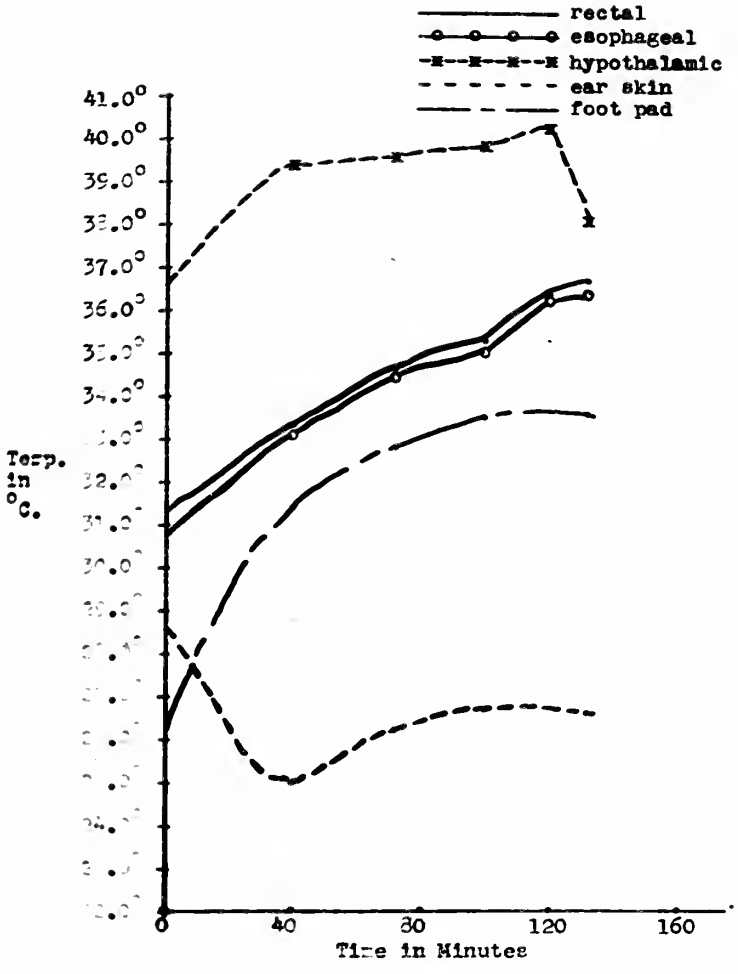


Figure 7

Rewarming of dog no. 5. Hypothalamic perfusion with water of 43.8° C. from 0 until 120 minutes.

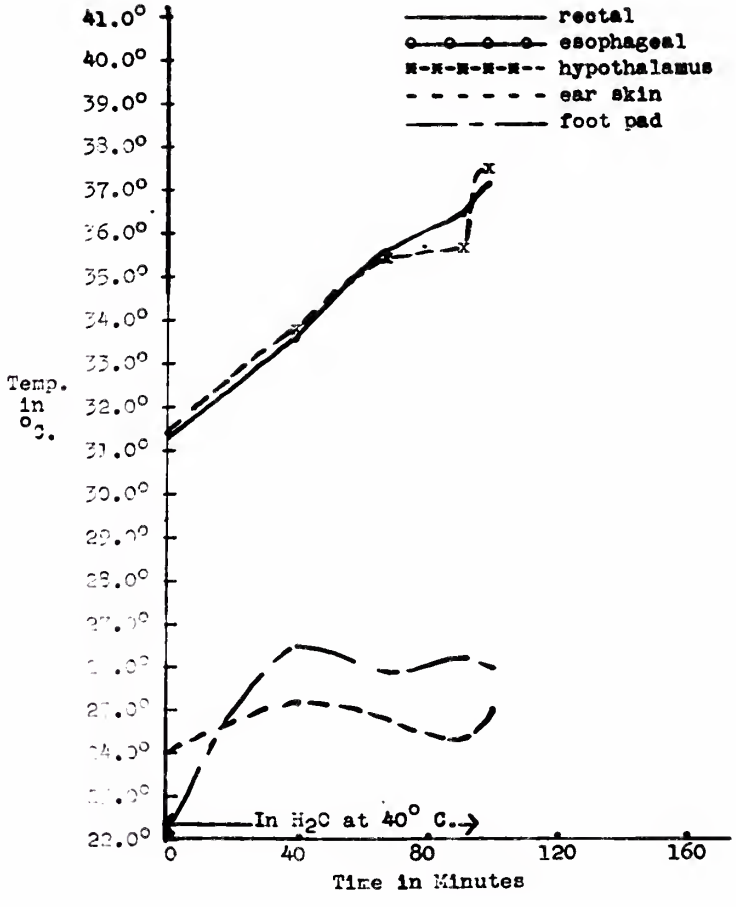


Figure 8

Rewarming of dog no. 5. Hypothalamic cooling with H_2O of 32.7° C. from 20 until 85 minutes.

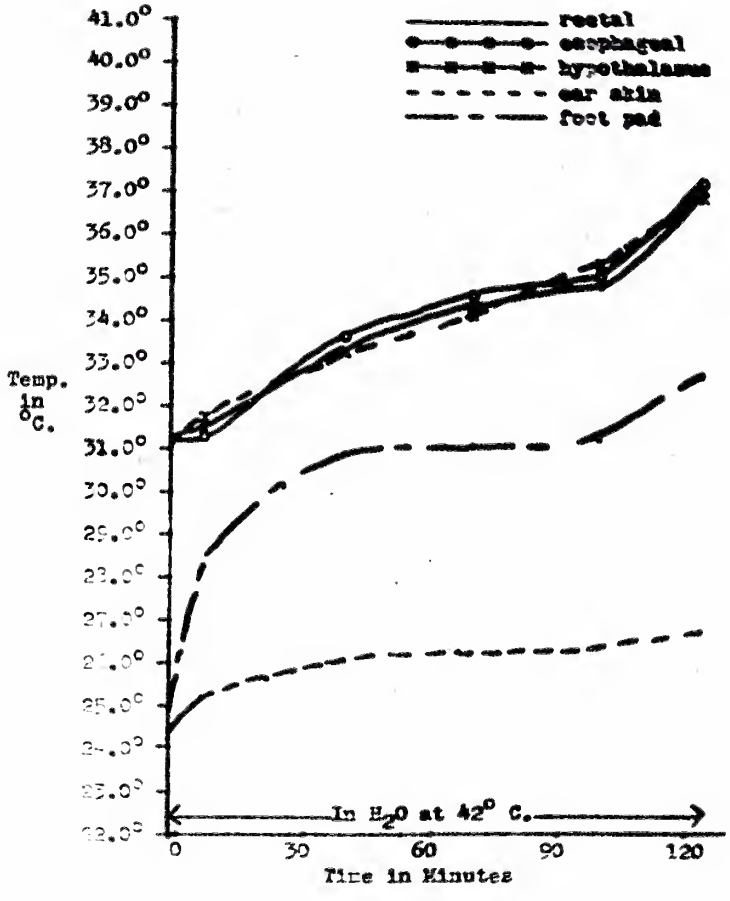


Figure 9

Rewarming of dog no. 5, with no hypothalamic perfusion (control rewarming).

Temp.	Dog No.	GROUP A Mid-Perfusion			GROUP B Initial Perfusion	GROUP C Control
		Before Perfusion	After Perfusion	Total Rate		
Rectum	1	.21	.15	.18	.23	.20
	2	.15	.28	.18	---	---
	3	.27; .24	.27; .26	.26	.24	.30
	4	.10	.11	.10	---	---
	5	.13	.14	.13	.14	.16
	Mean	.18 (S.D.=.07)	.20 (S.D.=.08)	.19 S.D.06	.21 (S.D.=.05)	.22 (S.D.=.07)
Esoph-agus	1	.23	.15	.19	.26	.22
	2	.14	.27	.17	---	---
	3	---	---	---	.25	.31
	3	.25	.28	.25	---	---
	4	.11	.10	.10	---	---
	5	---	---	---	.13	.16
	Mean	.18	.20	.18	.21	.23
Hypo-thala-mus	1	.23	.08	---	.18	.18
	2	.15	.17	---	---	---
	3	.26	.10	---	.18	.32
	3	.19	.07	---	---	---
	4	.11	.09	---	---	---
	5	.15,	.00	---	.11	.17
	Mean	.18	.10	---	.16	.20
Ear Skin	1	---	---	---	.33	.10
	3	.59	-.49	.16	.16	.53
	3	.14	-.13	.01	---	---
	4	.01	.01	.01	---	---
	5	.25	.00	.17	.16	.28
	Mean	.24	.09	.09	.22	.31
Foot Pad	1	---	---	---	.39	.37
	3	.39	.40	.40	.47	.18
	4	.21	.06	.17	---	---
	5	.25	.09	.20	.24	.22
	Mean	.29	.18	.26	.37	.13

Table 4

Rates of cooling in Part II for the three methods of cooling used. Temperatures are recorded in $^{o}C./Min/M^{2}$.

Temp.	Dog No.	Group A Hypothalamic Warming	Group B Hypothalamic Cooling	Group C Control
Rectum	1	.17	.14	.28
	2	.33	---	---
	3	.18	.18	.16; .14
	4	---	---	.09
	5	.08	.11	.08
	Mean	.19 (S.D.=.10)	.12 (S.D.=.01)	.15 (S.D.=.08)
Esoph-agus	1	.17	.15	.31
	2	.30	---	---
	3	.17	.12	---; .14
	4	---	---	.10
	5	.07	---	.09
	Mean	.18	.13	.16
Hypo-thala-mus	1	---	---	.33
	2	.18	---	---
	3	.09	.13	.18; .13
	4	---	---	.10
	5	.02	.11	.09
	Mean	.10	.12	.17
Ear Skin	1	.19	.02	---
	2	---	---	---
	3	.03	.12	.03; .02
	4	---	---	.02
	5	.02	.01	.04
	Mean	.08	.05	.03
Foot Pad	1	.08	.10	---
	2	---	---	---
	3	.05	.05	---; .16
	4	---	---	.04
	5	.10	.08	.13
	Mean	.07	.08	.11

Table 5

Rates of rewarming in Part II for the three methods of rewarming used. Temperatures are recorded in $^{o}C./Min/M^{2}$.

the rectum except when the hypothalamus was heated as the dog rewarmed. There was no consistent relationship between the ear skin and foot pad temperatures except in the control dogs, in whom the ear skin consistently rewarmed at a slower rate than the foot pad.

The first method of cooling, as described previously, was cooling the dogs to the mean rectal temperature of 33.8° C., then perfusing the hypothalamus with warm water as cooling was continued. To determine whether any observed differences in rates of cooling above and below the rectal temperature of 33.8° C. were significant, it was necessary also to calculate the rates of cooling of the rectum above and below 33.8° C. in the control dogs and in the dogs in whom hypothalamic perfusion with warm water was begun before cooling was started. These values are shown in Table 6.

Statistical comparison of the rates of cooling of the rectal temperature above and below 33.8° C. was carried out for each of the three groups. This was done using the following standard statistical formulas:

$$s^2 = \text{Variance} = \frac{1}{N-1}\left[\Sigma (x^2) - \bar{x}\Sigma(x)\right]$$

$$s^2_{\bar{x}} = \text{Variance of the mean} = \frac{1}{N} s^2$$

$$s_{\bar{x}} = \text{Standard deviation of the mean} = \frac{1}{\sqrt{N}} s$$

$$t = \frac{\bar{x}}{s_{\bar{x}}}$$

Rate of Cooling	Group A Mid-Perfusion in °C./Min/M^2	Group B Initial Perfusion in °C./Min/M^2	Group C Control in °C./Min/M^2
Above 33.8° C.	.18	.20	.24
Below 33.8° C.	.20	.22	.19
Total Rate	.19 (S.D.=.06)	.21 (S.D.=.05)	.22 (S.D.=.07)
Statistical significance of difference between rates of cooling above and below 33.8° C. ---expressed as P value.	.55	.15	.35

Table 6

Mean rates of cooling of rectum above 33.8° C., below 33.8° C., and the respective total mean rates of cooling. Statistical comparison, within each group, of rate above and below 33.8° C., expressed as P value. None of the differences are statistically significant.

These calculations showed that both the groups, A and B, which had hypothalamic perfusion, whether partial or complete, demonstrated a 0.02° C./Min/M^2 increase in rate of fall of rectal temperature below 33.8° C. This increase in rate was not statistically significant. In group C, the control series, there was a 0.05° C./Min/M^2 decrease in rate of fall of rectal temperature below 33.8° C., which also was not statistically significant.

The calculations described above were also used to compare the total rates of fall in temperature. Contrary to what was expected, the mean rate of fall of the rectal temperature in group B was 0.01° C./Min/M^2 less than in the control series (group C). This difference was not statistically significant, P being equal to .6. Also contrary to what was expected, the mean rate of fall for group A was 0.03° C./Min/M^2 less than the control series and this too was not statistically significant, P being equal to .3. Finally, the mean rate of fall in group A was 0.02° C./Min/M^2 less than in group B. This also was not statistically significant, P being equal to .6.

Although the control groups from Group I and Group II are not strictly comparable, the rates of fall of rectal temperature should, nevertheless, be essentially the same. For this reason, the two groups were compared statistically. The rate of fall of rectal tem-

perature was 0.04° C./Min/M^2 less in Group II controls than in Group I controls, but the difference was not statistically significant, P being equal to .65.

Another method of statistical comparison is the calculation of F Values. This is useful when there are several groups with the different results obtained for the same variable to be compared statistically. The calculation is valid only if each value obtained is an independent variable, and is statistically significant only if the differences within the groups are smaller than the differences between the groups. F Values were calculated, using the following groups: control series from Part I, test series from Part I, plus (1) group A from Part II, or (2) group B from Part II, or (3) group C from Part II. Three separate calculations were necessary because the values from the groups in Part II are not independent variables. This is because all these results were obtained on the same dogs.

F Values were calculated using the following formulas:[23]

$$F_{f1,f2} = \frac{(MS)_B}{(MS)_W}$$

$$(MS)_B = \frac{Sn_i(\bar{x}_i - \bar{X})^2}{f1}$$

f1 = number of groups - 1
n_i = number in each group
f2 = Sn_i - No. of groups
B = between groups
W = within groups
MS = mean square

$$(SS)_B = Sn_i(\bar{x} - \bar{X})^2$$

$$(SS)_W = \left[Sx^2 - \frac{(Sx)^2}{Sn_i}\right] - (SS)_B$$

$$(MS)_W = \frac{(SS)_W}{f2}$$

The calculated value for $F_{f1,f2}$ is then located in a table of F values to determine whether or not the differences between the groups are statistically significant. The results obtained are listed in Table 7.

The analysis of the rewarming experiments in Group II was done in a manner analagous to that in the cooling experiments. In Table 5, it can be seen that, using only rectal temperatures for statistical comparison, group A rewarmed at a faster rate than group B. However, this difference was not statistically significant, P being equal to .45. Group A also rewarmed faster than group C, but this difference was not significant either, P being equal to .65. Group B rewarmed at a slower rate than group C, but again the difference was not statistically significant, P being equal to .45. Although not strictly comparable, the rewarming control groups for Group I and Group II were also compared. The Group II controls rewarmed at a slightly faster rate, but the difference was not statistically significant, P being equal to .7. Finally, F values were calculated for the rewarming experiments. These results are shown in Table 8.

Groups: Part I Control dogs Part I Test dogs Plus:	$F_{f1,f2}$	Statistical Significance
A. Part II Mid-perfusion	$F_{2,12}=2.89$	None
B. Part II Full perfusion	$F_{2,10}=3.33$	None
C. Part II Control dogs	$F_{2,10}=3.65$	None

Table 7

Results of F value calculations for cooling. No statistically significant differences were observed.

Groups: Part I Control Dogs Part I Test Dogs Plus:	$F_{f1,f2}$	P Value
A. Part II Hypothalamic warming	$F_{2,10}=4.90$	P less than .05
B. Part II Hypothalamic cooling	$F_{2,9}=17.6$	P less than .01
C. Part II Control dogs	$F_{2,10}=3.39$	Not Significant

Table 8

Results of F value calculations for rewarming.

DISCUSSION

The facts as regards the present state of knowledge of the physiology of temperature regulation can best be understood by summarizing some of the experimental data. The study of experimental lesions has clearly implicated the hypothalamus, spinal cord and the intervening connecting pathways, the latter including the vasomotor, respiratory, and voluntary motor systems, as the parts of the central nervous system most involved in temperature regulation. In addition, the cortex and all other portions of the central nervous system are thought to have important roles in the normal regulation of body temperature. It also has been possible with experimental lesions to differentiate, at least partially, the cold responses from the heat responses and to demonstrate the widespread locations of structures in the brain stem and spinal cord which have some powers to take over regulatory activity in the absence of higher connections.[1,4,6,24]

By implanting small gold foil electrodes on the ventral brain surface in contact either with the anterior or posterior hypothalamus of dogs, Hemingway demonstrated that clear-cut thermo-regulatory responses can be obtained in the unanesthetized animal by local hypothalamic heating and without in any way damaging

the sensitive structures by insertion of needles or electrodes.[14] In this study, heating the posterior hypothalamus had comparatively little effect.

In a warm environment, local cooling of the anterior hypothalamic region of the dog caused a marked vasoconstriction, but in a cool or neutral environment such associated changes in blood flow could not be observed. Using this same experiment, Strom and Folkow also observed that the temperature elevation required to evoke panting was higher than that causing vasodilatation, indicating a differential threshold for the two responses in the central structures as has been found previously for heating the skin.[5,26,27,28]

Using permanently implanted electrodes, many investigators have observed that the over-all result of local heating of the preoptic area to 39° to 41° C. was a lowering of the internal body temperature.[7,8,10,12] This response was determined to a great extent by the external temperature. In a cool environment (14° C.) there was a decrease in metabolic rate associated with periodic complete cessation of shivering. Local cooling of the anterior hypothalamus in the same location where it was heated induced shivering when the dog was in a neutral environment. In none of the experiments with heating or cooling was it possible to drive the internal body temperature beyond certain

limits. The greatest rise in rectal temperature it was possible to obtain with continued vigorous cooling of the hypothalamus (circulating water temperature of 32° C.) was 0.5° to 1.0° C. and the greatest decrease produced even by prolonged heating was 1.0° to 2.5° C.. This indicates that the hypothalamic regions which are being heated or cooled are not the only thermal inputs into the regulatory system; also, peripheral thermal effects may limit the extent to which the central thermal stimulation is effective in altering body heat content. In the area of the hypothalamus there are, therefore, neurons thermally sensitive both to heating and to cooling. The probable location of the structures sensitive to heating, and possibly also the structures sensitive to cooling, is primarily in the area immediately ventral to the anterior commissure. The action of the temperature changes imposed on the central structures is that which is essential to a thermostat, i.e., the action tends to reduce the thermal displacement and thus has the character of a negative feedback.

At present, then, the generally supported concept of the physiology of temperature regulation is that there are two "centers," one for heat and the other for cold (the former in the anterior hypothalamus and the latter in the posterior hypothalamus), which are stimulated locally by the temperature of the blood.[13]

These hypothalamic "centers" are thought to regulate heat loss and heat production by mutual inhibition of activity. It is assumed that the receptors of the hypothalamus respond with both phasic and static responses to temperature as do the peripheral receptors. The "set point" for this area is established basically by the difference in the static firing rates of the hypothalamic cold and warmth receptors.

In short, temperature is the regulated variable and the temperature receptors of the skin, hypothalamus and other body areas have somewhat similar properties and participate in this regulation. The combined effects of the cold and warmth receptors prescribe in some as yet undetermined additive manner the action of the thermoregulator; this regulator has the properties of proportional and rate control, but not integral control. The zones of regulation can be differentiated into vasomotor control (neutral zone), evaporative and vasomotor control (hot zone), and control of metabolic rate (cold zone). The regulation of the body temperature in the cold and neutral zones is primarily effected by the action of the peripheral receptors, whereas regulation in the hot zone and during activity appears to be more under the control of the central receptors.

Homeothermic animals have five primary physiologic defenses against cold: (1) behavioral responses which

influence an animal to seek a comfortable thermal environment, (2) piloerection, (3) nonshivering thermogenesis, (4) shivering, and (5) the thermal cutaneous vasomotor response, which results in cutaneous vasoconstriction induced by cold.[15] All of these defenses are, of course, either controlled or influenced by the central nervous system. Of these five, the latter two are the ones relevant to clinical hypothermia and therefore the ones of importance here.

When an animal is exposed to a cold stimulus, its rate of cooling must, perforce, represent an interplay of two opposing physiologic forces, namely, heat loss and heat production. Those workers in the field of hypothermia who emphasize the need of inhibiting shivering as a prerequisite for faster cooling rates do so on the premise that decreased heat production is very important. This line of reasoning, emphasizing the negative influence of shivering on cooling rates, predominates in the research done in the field of hypothermia.

Shivering is the primary contributor to elevated heat production when an animal is suddenly exposed to a cold environment. Shivering can increase oxygen consumption 400 per cent, while the contributions of nonshivering thermogenesis are less than 100 per cent and generally thought to be less than 25 per cent.[4,21] Shivering, then, apparently represents a physiological

resistance to cooling in hypothermia; that is, if the anesthesia is not deep enough, there is an attempt to maintain the temperature of the body by muscular movements; these begin as fine tremors and, if allowed to do so, go on to definitive shivering.[22] In short, if this line of reasoning is correct then fall in body temperature is relatively slow when shivering and rhythmical movements occur. It is commonly believed, therefore, that anesthesia alone will facilitate cooling by abolishing the shivering mechanism.

Surgical anesthesia was achieved in our experiments by the use of sodium pentothal, a barbiturate anesthetic. The amount and frequency of reinforcement doses was determined by the presence or absence of shivering. That is, whenever any potential indication of shivering occured, a reinforcement dose was given. Another obvious means of inhibiting shivering, which was not done here, would be to use curare to produce complete muscle relaxation.

Anesthesia and various drugs have been employed to counteract the body's two primary defenses against hypothermia, namely, vasoconstriction and shivering. Shivering, as has been mentioned, does increase heat production. The effect of vasoconstriction is to decrease heat loss. Therefore, it has long been argued that rates of cooling would be greater if

peripheral vasoconstriction were prevented by the use of anesthetics and/or vasodilator drugs. Despite many attempts, there now seems to be very little direct evidence of drug-induced vasodilatation during the active phase of surface cooling in hypothermia.[25] Many anesthetic drugs, however, are vasodilators, and pentothal is no exception. Due to this vasodilatory effect of pentothal, in almost all of the animals in these experiments in whom skin temperatures were monitored, at least the ear skin temperature was relatively high following pentothal induction and in the earliest (inactive) phase of cooling. These initial skin temperatures, in the 30° to 36° C. range, indicate significant peripheral vasodilatation. No readings were taken before pentothal induction, which would have been necessary in order to prove that this was a direct effect of the pentothal; nevertheless, it is apparent that most of the dogs demonstrated peripheral vasodilatation prior to cooling and this was probably due to the pentothal anesthesia. However, this initial vasodilatation was readily counteracted by the surface-cooling, for the skin temperatures fell precipitously as the hypothermia progressed. Thus, the peripheral vascular tone was more dependent on the effects of the surface-induced hypothermia (i.e., skin temperature) than on the pharmacological properties of pentothal.

A complete analysis of the relationships of surface cooling to peripheral vascular tone is, of course, not possible solely on the basis of the data presented here, for no temperatures were recorded of skin that was immersed in the ice water. However, it is evident that, in terms of rates of cooling, neither pentothal nor hypothalamic perfusion with warm water had any significant effect on peripheral vascular tone.

The hypothesis which formed the basis for our experiments was that increased rates of cooling could be achieved by simultaneous hypothermic perfusion with warm water, thereby increasing heat loss by sustaining peripheral vasodilatation. Fundamental to this hypothesis was the acknowledged importance of peripheral blood flow in terms of rates of heat loss. Experiments by Mellinger demonstrated that heat production (shivering) exerted only a minor effect on cooling rate and that heat exchange at the body surface was the important factor during the induction of hypothermia.

Mellinger carried out two separate sets of experiments.[19,20] In his first experiments, rabbits, guinea pigs and rats were surface-cooled in ice water in the following ways: (1) with maximum exercise (forced to swim), (2) restrained, (3) killed and immediately cooled (i.e., without peripheral circulation or muscular activity), and (4) with pentobarbital.

He also performed experiments to compare rates of cooling between (a) ether and pentobarbital, (b) curare and anectine, and (c) alcohol and thorazine. Mellinger found, contrary to what is commonly believed, that a stepwise reduction in muscular activity or full relaxation by a barbiturate did not shorten but actually prolonged the cooling time. There were no significant differences among the anesthetics tested, but the cooling time was prolonged with all the anesthetics. Furthermore, no animal exhibited a greater cooling rate treated with a muscle relaxant than untreated and restrained in a wire screen. There were no differences between the controls and those treated with alcohol or thorazine. Lacking, however, was a comparison between animals treated with a barbiturate and with curare. Mellinger concluded (1) that statements to the effect that thermoregulatory defense mechanisms must be suppressed before cooling in order to produce adequate induction of hypothermia could not be confirmed, and (2) that lack of circulation on the body surface reduces the cooling rate whereas maximal muscular activity leads to maximal peripheral blood flow and therefore transforms the body shell into a good heat exchanger.

Mellinger performed a second set of experiments using the same methods but this time measuring oxygen consumption. As previously, the swimming, unanesthetized

animals cooled the fastest, the unanesthetized, restrained animals less rapidly, the barbiturate animals very slowly, and postmortem animals the slowest. He found an obviously higher oxygen consumption in the more exercised animals but the greater the heat production, the greater also was the rate of cooling. Measuring the heat production, it was found to be very small compared to the heat loss. The small heat production was not, therefore, an effective means of hindering the heat loss, for the animals under deep anesthesia required twice the time to reach a core temperature of 25° C. as the swimming animals.

The mechanism of blood flow and thermal exchange at the skin surface is not yet understood. As demonstrated by Mellinger, heat loss is probably the important factor. The skin can thus be considered to be a heat exchanger and the rate of cooling to be dependent on peripheral blood flow. The question then becomes one of what is the best means of producing a better blood flow at the periphery. Recognizing the importance of maximal peripheral blood flow, it was our assumption that this could be achieved by controlling the central reflex mechanisms. Mellinger's work indicates, on the other hand, that exercise is the most effective method of increasing peripheral blood flow and thereby increasing heat loss. An

important missing link is a study comparing rates of cooling in untreated animals and animals treated with a barbiturate and with curare. This comparison is not available and is necessary before we can conclude definitely that neither heat production nor central reflex mechanisms can influence rates of inducing hypothermia in surface-cooled animals.

Following the completion of these experiments and of the statistical analyses, we thought it would be useful to know whether nonshivering thermogenesis or unrecognized shivering might have had any effect on the data obtained. Accordingly, the data already presented was statistically compared to a group of dogs in which cooling was done with curare rather than a barbiturate anesthetic.[29] In these experiments, the dogs were given 35 mg./Kilo. of pentothal, following which the trachea and blood vessels were cannulated; then, 10 per cent of the calculated lethal dose of curare was administered, followed by 1.8 per cent of the lethal dose each hour until the end of the experiment. One hour after the single dose of pentothal was given, by which time its effect had disappeared, the dogs were placed in an ice bath and cooled to a rectal temperature of 29° C. When this temperature was reached the dogs were taken out of the ice bath, at which time their metabolic rate was 52 per cent of

normal, wrapped in blankets and allowed to rewarm spontaneously. Werner intended to demonstrate nonshivering thermogenesis in these experiments. However, for reasons which are not important here, this was not achieved. Suffice it to say that as yet nonshivering thermogenesis has been observed only in rats. The results of Werner's experiments are shown in Table 9.

The relevance of Werner's data to the experiments presented here is that since the cooling itself was done under identical conditions, the rates of cooling, corrected for body surface area, should be similar. However, when the curare dogs are compared to the Group II controls, the curare dogs are shown to cool at a much faster rate, this difference being statistically significant, with P less than .01. Similarly, if the curare dogs are included in the calculation of F values as shown in Table 7, the differences between the three groups becomes statistically significant, P being less than .01. In short, there is a significant, unexplained difference in the rates of cooling between the pentothal and curare dogs.

The only apparent difference between the curare dogs and the Group II controls was the choice of anesthetic agent. Since the curare dogs (not under the influence of pentothal) obviously could not shiver, and the Group II controls (under the influence only of

Dog No.	Weight in Kg.	Body Surface Area in M^2 ($A = KW^{2/3}$)	Rate of Cooling Rectal Temperature in $^{o}C./Min/M^2$
1	20.2	.82	.39
2	18.2	.76	.33
3	18.0	.76	.32
4	14.8	.67	.54
5	15.8	.69	.46
6	15.3	.68	.47
7	14.8	.67	.31
8	14.6	.66	.62
9	16.0	.70	.31
Mean	16.4	.71	.41
S.D.	2.0	.05	.13

Table 9

Results of surface-cooling in dogs receiving only curare. Data reported by Werner.

pentothal) cooled at a significantly slower rate, the most obvious conclusion is that this difference is due to the presence of nonvisible shivering in the pentothal-cooled animals. The assumption that such unrecognized shivering did occur in the pentothal-cooled animals does not alter the validity of the comparisons between these dogs because the degree of unrecognized shivering was relatively constant in each experiment, but it is evident that if one wants to determine absolute rates of cooling, this cannot be done using a barbiturate alone unless large doses are used. Nevertheless, the fact remains that we cannot adequately explain the difference in rates of cooling between Werner's and our control experiments. There may be factors which are not apparent as of now and which would explain the differences, but in the absence of such factors we can only conclude that the final answer is not yet available and that a study is needed in which rates of cooling are compared in animals untreated, treated with a barbiturate and treated with curare. Only then can we reconcile Werner's, Mellinger's and our data.

A question which can be at least partially answered by comparing the pentothal-cooled to the curare-cooled animals is the question of the effect of anesthesia on the animal's temperature regulatory mechanisms.

Pentothal, in addition to its vasodilatory effect, is known to cause depression of the cerebral cortex and probably also the thalamus.[17] A third, albeit minimal, effect is a slight decrease in basal metabolic rate, which probably would result in a slight decrease in body temperature. In short, the actions of pentothal tend to paralyze temperature control mechanisms and to lower the internal body temperature slightly. This was readily observable in all of the dogs used in Group II. In contrast to this, curare acts only to inhibit striated muscle activity, with no effect whatsoever on temperature regulatory capacities. The curare dogs, then, with intact temperature control centers, still have the ability to resist a lowering of body temperature as compared to the pentothal-cooled dogs. Since the curare dogs did not cool at a slower rate, however, it is evident that this was not an important factor.

Present data suggests that both peripheral and central influences affect the control of the cutaneous vascular system and the transfer of heat into it. The most significant peripheral influence is the local skin temperature insofar as total cutaneous blood flow is concerned. The effects of central temperature on the vasomotor control of the cutaneous blood vessels is often obscurred by other influences acting on them.[15]

As discussed by Benzinger, under normal conditions the anterior hypothalamus activates the heat loss responses and also shapes, by central counteraction, the adequate response of increased metabolic heat production to cold reception at the skin.[2] In alert, unanesthetized dogs, then, the mechanism of physical temperature regulation consists of physiologically meaningful and reproducible responses to warm stimulation of the internal thermoreceptive system. Whether these mechanisms are operative when exposed to unphysiologic temperatures and compounded by surgical anesthesia is, of course, a basic and important question.

The intention of our experiments was to attempt to alter the central temperature as perceived by the hypothalamus such that cutaneous blood flow would remain at a higher level than in control animals. As can be seen by referring to the graphs of ear and foot pad temperatures, however, hypothalamic temperature had no effect on the skin temperatures. This is taken to mean that hypothalamic heating had no effect on cutaneous blood flow. It is well established that in unanesthetized animals, a physiologic change in hypothalamic temperature will affect cutaneous blood flow. It was hypothesized that this might occur in anesthetized dogs so that heat would be lost to the environment at a faster rate. However, no such temperature

regulatory function could be demonstrated in these anesthetized animals. As noted previously, the control dogs in Group II cooled at the fastest rate, contrary to what was anticipated. At first, it was thought that the slower rates of cooling in the dogs with hypothalamic heating could conceivably have been due simply to the thermal input secondary to hypothalamic perfusion. However, if this were true, then the full perfusion dogs should cool at a slower rate than the mid-perfusion dogs (Table 6) since the thermal input in the former was less, which is the exact opposite of what did in fact occur.

It has been established, then, that hypothalamic influences could not affect cutaneous blood flow in these experiments. Afferent impulses from the skin, however, such as direct thermal effects on blood vessels and axone reflexes resulting from thermal stimulation of the skin, may have been important. That is, peripheral influences are not minor and may dominate a particular situation.[15] Nevertheless, the fact remains that temperature regulatory capacities were not demonstrated in these animals and, as a result, local heating of the hypothalamic temperature control centers had no effect on the rate of induction of hypothermia.

SUMMARY AND CONCLUSION

The present experiments were designed to demonstrate the presence of temperature control mechanisms in anesthetized animals that would affect the rates of inducing hypothermia in surface-cooled dogs. Any positive effect would be mediated through changes in cutaneous blood flow and it was postulated that raising hypothalamic temperatures above the set point would lead to greater cutaneous blood flow and hence to a greater rate of heat loss.

The results obtained indicate that there were no statistically different rates of cooling among the groups and, in fact, that the control groups, contrary to what was postulated, were the ones which cooled faster, although not significantly faster. However, all the rates of cooling were significantly slower than those in a group of dogs (reported by Werner) in which a complete lack of muscular activity was produced by the use of curare. A discussion of these and other experimental results indicates that the effect of shivering on rates of cooling is not clear and further work is suggested. The following conclusions can be made:

1. No changes in peripheral blood flow could be produced by our experimental method.

Therefore, the primary role of heat loss in producing greater rates of cooling in surface hypothermia could not be confirmed.

2. The present experiments provide further evidence for the absence of temperature regulatory mechanisms in anesthetized animals.
3. The results obtained in the present experiments further indicate that, in the absence of central temperature regulatory mechanisms, peripheral factors are predominant, are relatively constant in anesthetized surface-cooled animals, and are unaffected by artificially induced changes in hypothalamic temperature.

BIBLIOGRAPHY

1. Anand, B.K., and Brobeck, J.R. Hypothalamic control of food intake in rats and cats, Yale J. Biol. and Med., 24:123, 1951.
2. Benzinger, T.H., Kittzinger, C., and Pratt, A.W. The human thermostat, in Temperature, Vol. Three, ed. by J.D. Hardy, New York, Reinhold Publishing Company, 1963, p. 637.
3. Clark, G., Magoun, H.W., and Ranson, S.W. Hypothalamic regulation of body temperature, J. Neurophysiol., 2:61, 1939.
4. Dill, D.B., and Forbes, W.H. Respiratory and metabolic effects of hypothermia, Am. J. Physiol., 132:685, 1941.
5. Folkow, B., Strom, G., and Uvnas, B. Cutaneous vasodilatation elicited by local heating of anterior hypothalamus in cats and dogs, Acta Physiol. Scand., 17:317, 1949.
6. Frazier, C.H., Alpers, B.J., and Lewy, F.H. Anatomical localization of hypothalamic centre for regulation of temperature, Brain, 59:122, 1936.
7. Fusco, M.M. Calorimetric measurements of physiological responses of conscious dog to local heating of anterior hypothalamus, Physiologist, 1:25, 1958.
8. _____ Responses to local heating of hypothalamus, Ph.D. Thesis, Univers. Penn., 1959.
9. Glenn, W.W.L., Stolwijk, J.A.J., Annamunthodo, H., Rapp, G.M., and Himmel, M. An integral fin-type blood heat exchanger, Surgical Forum, 10: 574, 1960.
10. Hammel, H.T., Fusco, M.M., and Hardy, J.D. Responses to hypothalamic cooling in conscious dogs, Federation Proc., 18:63, 1959.
11. _____ Jackson, D.C., Stolwijk, J.A.J., and Hardy, J.D. Hypothalamic temperatures in dog and monkey and thermoregulatory responses to environmental factors, Technical Documentary Report No. AMRL-TDR-63-5, Jan., 1963.
12. Hardy, J.D., Fusco, M.M., and Hammel, H.T. Responses of conscious dog to local heating of anterior hypothalamus, Physiologist, 1:34, 1958.
13. _____ Physiology of temperature regulation, Physiol. Reviews, 41:521, 1961.
14. Hemingway, A., Rasmussen, T., Wikoff, H., and Rasmussen, A.T. Effects of heating hypothalamus of dogs by diathermy, J. Neurophysiol., 3:329, 1940.

15. _____, and Stuart, D.G. Shivering in man and animals, in Temperature, Vol. Three, ed. by J.D. Hardy, New York, Reinhold Publishing Company, 1963, p. 407.
16. Kleiber, M. The fire of life, John Wiley & Sons, Inc., 1961, p. 184.
17. Krantz, J.C., and Carr, C.J. Pharmacological principles of medical practice, Baltimore, Williams & Wilkins, 1961, p. 607.
18. Lewis, F.J. Hypothermia, Internat. Abstr. Surgery, 113:307, 1961.
19. Mellinger, T.J. Heat loss and heat production during induction of hypothermic anesthesia, Ann. Surg., 161:131, 1965.
20. _____ Muscle relaxants and cooling rate in hypothermic anesthesia, Ann. Surg., 152:1078, 1960.
21. Muller, W.H., and Dammann, J.F. Problems in methods of inducing hypothermia by external cooling, in Physiology of induced hypothermia, NAS-NRC 451, 1956, p. 415.
22. Simpson, S., and Herring, R.J. The effect of cold narcosis on reflex actions in warm-blooded animals, J. Physiol., 32:305, 1905.
23. Snedecor, G.W. Statistical methods, Ames, Iowa, Iowa State University Press, 1956.
24. Spencer, F.C., and Bahnson, H.T. The present role of hypothermia in cardiac surgery, Circulation, 26:292, 1962.
25. Spurr, G.B. Techniques for inducing hypothermia, in Temperature, Vol. Three, p. 495.
26. Strom, G. Effect of hypothalamic cooling on cutaneous blood flow in the unanesthetized dog, Acta Physiol. Scand., 21:271, 1950.
27. _____ Influence of local thermal stimulation of the hypothalamus of the cat on cutaneous blood flow and respiratory rate, Acta Physiol. Scand., 20:47, 1950.
28. _____ Influence of skin temperature on vasodilator response to hypothalamic heating in the cat, Acta Physiol. Scand., 20:77, 1950.
29. Werner, A.Y., Dawson, D., and Hardenbergh, E. Spontaneous rewarming of hypothermic curarized dog, Science, 124:1145, 1956.

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